PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000915	09.03.2005	09.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D519/00, A61K31/5517, A61P35/00, A61P31/04

Applicant
SPIROGEN LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12, 13-15 (partly) (with regard to industrial applicability)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 12, 13-15 (partly) (with regard to industrial applicability)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-11, 13-15 (partly)
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 12 and claims 13-15, as far as they refer to the method of claim 12, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Cited documents

D1: WO 00/12508 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION; THURSTON, D) 9 March 2000 (2000-03-09)

D2: WO 00/12507 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION; THURSTON, D) 9 March 2000 (2000-03-09)

D3: WO 93/18045 A (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED) 16 September 1993 (1993-09-16)

D4: GREGSON S J ET AL: "Design, Synthesis, and Evaluation of a Novel Pyrrolobenzodiazepine DNA-Interactive Agent with Highly Efficient Cross-Linking Ability and Potent Cytotoxicity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 5, 2001, pages 737-748, XP002272009 ISSN: 0022-2623

D5: GREGSON S J ET AL: "Synthesis of the first example of a C2-C3/C2'-C3'-endo unsaturated pyrrolo[2,1-c][1,4]benzodiazepine dimer" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 21, 27 August 2001 (2001-08-27), pages 2859-2862, XP002329276 ISSN: 0960-894X

D6: GREGSON S J ET AL: "SYNTHESIS OF A NOVEL C2/C2'-EXO UNSATURATED PYRROLOBENZODIAZEPINE CROSS-LINKING AGENT

WITH REMARKABLE DNA BINDING AFFINITY AND CYTOTOXICITY" CHEMICAL COMMUNICATIONS - CHEMCOM, ROYAL SOCIETY OF CHEMISTRY, GB, no. 9, 1999, pages 797-798, XP001156959 ISSN: 1359-7345

D7: KAMAL A ET AL: "Synthesis of pyrrolo[2,1-c][1,4]benzodiazepines via reductive cyclization of omega-azido carbonyl compounds by TMSI: an efficient preparation of antibiotic DC-81 and its dimers" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 20, 16 October 2000 (2000-10-16), pages 2311-2313, XP004224207 ISSN: 0960-894X

D8: SAGNOU M J ET AL: "Design and synthesis of novel pyrrolobenzodiazepine (PBD) prodrugs for ADEPT and GDEPT" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 18, September 2000 (2000-09), pages 2083-2086, XP004208317 ISSN: 0960-894X

D9: THURSTON D E ET AL: "Synthesis of Sequence-Selective C8-Linked Pyrrolo[2,1-c][1,4]benzodiazepine DNA Interstrand Cross-Linking Agents" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 61, no. 23, 1996, pages 8141-8147, XP002272010 ISSN: 0022-3263

The indicated designations will be adhered to throughout the examination procedure.

V.2 Novelty

V.2.1 The subject-matter of claim 1 is generically disclosed in D3, claims 1 and 2. However, D3 does not disclose a specific example which falls under the formula of present claim 1: The compound of example 4 of D3 does not have ethylidene groups, and the compound of example 6 of D3 has a linking alkylene group of three C atoms only. Therefore the subject-matter of claims 1-15 on file is novel with regard to D3.

V.2.2 None of the compounds disclosed in D1, D2 and D4-D9 have ethylidene groups and/or a linking group of five C atoms. Therefore the subject-matter of claims 1-15 is novel over D1, D2 and D4-D9.

V.3 Inventive step

V.3.1 According to the description, the problem underlying the present application can be seen in the provision of compounds similar to those disclosed in D3, the compounds being useful in the treatment of gene-based diseases, which includes cancer and bacterial infections.

V.3.2 D3 is considered to represent the closest prior art since it generically discloses the present compounds. The compounds of D3 have similar activity, especially activity against cancer is mentioned in D3. D1 and D2 disclose similar compounds, and these compounds are described to exhibit activity against cancer **and** against bacterial infections.

V.3.3 The skilled person, faced with the technical problem as defined above, would certainly structurally modify, with the expectation of success, the preferred (concretely mentioned) compounds of the relevant prior art. By the combination of the structural features of example 4 of D3 (having a pentanediyl linker) and of example 6 of D3 (having ethylidene groups at the five-membered heteroring), the person skilled in the art directly arrives at the present compounds so that it must be said that the presently claimed compounds are structurally obvious in view of the disclosure of D1. It is evident from D1 that the compounds thus obtained would also have anticancer activity, and from D1, disclosing structurally similar compounds, the skilled person deduces that such compounds should also have antibacterial activity. Consequently, the person skilled in the art would test the compounds with regard to antibacterial activity, too. The finding that the present compounds have activity against gram-positive bacteria, cannot be considered as to be unexpected, at least with the combined knowledge of D3 and D1.

V.3.4 Therefore, at the moment the presence of an inventive step cannot be acknowledged for the subject-matter of claim 1. The dependent claims 2 to 7 do not appear to introduce any technical features which would allow to acknowledge an inventive step either. Because the pharmaceutical use of the compounds is also obvious with regard to D3 and D1 (see above), claims 9 to 15 are not considered inventive either. As to claim 8 (process claim), it is noted that there is no technical feature how the synthesis of the compounds could be carried out. It is moreover stressed that processes for the preparation of similar compounds are already known from e.g. D3. Consequently, no inventive step cannot be acknowledged for claim 8 either.

V.4 Industrial applicability

V.4.1 The subject-matter of claims 1-11 and of claims 13-15, as far as they refer to the use of claim 11, are considered to be industrially applicable.

V.4.2 For the assessment of the present claim 12 and of present claims 13-15, as far as they refer to the method of claim 12, on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII
Certain defects in the international application

Claims 13-15 each belong to two categories of claims (process claim and use claim). It is stressed that each claim should only belong to one category.

Re Item VIII
Certain observations on the international application

VIII.1 In claim 1, the term "protecting group" is unclear since the very subject-matter for which protection is sought is not clearly defined (Art. 6 PCT). Even "carbamate" as definition of "protecting group" in claim 4 does not clearly identify which groups are included. Moreover, it is not clear from claim 1 if the compounds containing a "protecting group" are to be considered as end products or as intermediates. Intermediates normally do not have the desired activity that the end products have. Therefore it is not clear whether the protected compounds of claim 1 also solve the problem underlying the

application. If the protected compounds are to be considered as intermediates, they should have been claimed, for the sake of clarity, in an extra claim.

VIII.2 Claim 8 is unclear as to the very subject-matter for which protection is sought since it does not comprise any technical features which would explain how the synthesis of the compounds of claim 1 could be executed.